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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/529,130	06/22/2000	MICHAEL JOHN DUGGAN	1581.0580000	2901

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EXAMINER
KAM, CHIH MIN

ART UNIT	PAPER NUMBER
1653	14

DATE MAILED: 03/19/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/529,130	DUGGAN ET AL.	
	Examiner	Art Unit	
	Chih-Min Kam	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 December 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16,18-54 and 57-62* is/are pending in the application.

4a) Of the above claim(s) *57 and 62* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16,18-54 and 58-61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *11,13* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of the Claims

1. Claims 1-16, 18-54 and 57-62 are pending.

Applicants' amendment filed on December 14, 2001 (Paper No. 12) is acknowledged and applicants' response is fully considered. Claims 1-13, 15, 16, 18-34, 36-43, 46-49, 51 and 52 have been amended, claim 17 has been cancelled, and new claims 58-62 have been added. Claim 17 and its dependent claim 62 stand withdrawn from consideration because they are non-elected claims. Thus, claims 1-16, 18-54 and 58-61 are examined.

Objection Withdrawn

2. The previous objection to the Specification regarding the term "Example 6", is withdrawn in view of applicants' amendment to the specification in Paper No. 12.

Rejection Withdrawn

Claim Rejections - 35 USC § 112

3. The previous rejection of claims 1-54, under 35 U.S.C. §112, second paragraph, regarding the term "a derivative of a clostridial neurotoxin", "L-chain or a fragment thereof", "is derived from", "non-clostridial source", "recombinant technology", "modified", "modification", or "clostridial neurotoxin-derived component" is withdrawn in view of applicants' amendment to the claim, applicants' cancellation of claim 17 and applicants' response at pages 34-38 in Paper No. 12.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-16, 18-54 and 58-61 are rejected under 35 U.S.C. 112, first paragraph because the specification, while being enabling for an agent (lectin-LH_N) comprising a galactose-binding lectin covalently linked to a fragment of clostridial neurotoxin (LH_N, where L is light chain or its functional fragment, and H_N is a membrane translocation domain), a method for obtaining the agent, or a method of controlling the transmission of sensory information or the sensation of pain by administering the agent, or, for an agent of LH_N linked to lectin, an agent of a modified clostridial neurotoxin having H_C chemically modified to reduce its ability to bind the receptor, linked to lectin, an agent of a hybrid molecule of a modified heavy chain of a clostridial toxin with a light chain of a different clostridial toxin, linked to lectin, or a fusion protein of the agent expressed recombinantly as indicated in the prior art, does not reasonably provide enablement for an agent comprising a galactose-binding lectin or a modified galactose-binding lectin, the L chain of a clostridial toxin or its functional fragment, and a membrane translocation domain, wherein the three components are linked together, a method for obtaining the agent and a method of controlling the transmission of sensory information or the sensation of pain by administering the agent. The specification does not enable a person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 1-16, 18-54 and 58-61 are drawn to an agent comprising a galactose-binding lectin or a modified galactose-binding lectin, the L chain of a clostridial toxin or its functional fragment, and a membrane translocation domain, wherein the three components are linked together (claims 1-16 and 18-45), a method for obtaining the agent (claims 46-50) and a method

of controlling the transmission of sensory information or the sensation of pain by administering the agent (claims 51-54 and 58-61). The specification, however, only discloses cursory conclusions (page 4, line 17-page 5, line 10; page 9, line 28-page 10, line 33), which state an agent of a galactose-binding lectin or a modified galactose-binding lectin, the L chain of a clostridial toxin or its functional fragment, and a membrane translocation domain, wherein the three components are linked together, can be obtained by chemically coupling or recombinant expression as a fusion protein, and the agent can reduce and prevent the transmission of pain signals from nociceptive afferents to projection neurons. There are no indicia that the present application enables the full scope in view of the agent of a galactose-binding lectin, the L chain of a clostridial toxin or its functional fragment, and a membrane translocation domain as discussed in the stated rejection. The present application provides no indicia and no teaching/guidance as to how the full scope of the claims is enabled. The factors considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d at 731,737, 8 USPQ2d at 1400,1404 (Fed. Cir.1988)). The factors most relevant to this rejection are the breath of the claims, the absence of working examples, the state of the prior art and relative skill of those in the art, the unpredictability of the art, the nature of the art, the amount of direction or guidance presented, and the amount of experimentation necessary.

(1). The breath of the claims:

The breath of the claims is broad and encompasses unspecified variants regarding the modified galactose-binding lectin, the membrane translocation domain, and the linkage of three components, which are not adequately described or demonstrated in the specification.

(2). The absence of working examples:

There are no working examples indicating the claimed methods in association with the variants except ExL-LH_N/A, EcL-LH_N/A and SBA-LH_N/A.

(3). The state of the prior art and relative skill of those in the art:

The prior art (Foster *et al.*, WO 96/33273) has indicated an agent of LH_N, a modified clostridial neurotoxin having H_C chemically modified to reduce its ability to bind the receptor, or a hybrid molecule of a modified heavy chain of a clostridial toxin with a light chain of a different clostridial toxin, being linked to lectin, or a fusion protein of the agent expressed recombinantly. However, the general knowledge and level of the skill in the art do not supplement the omitted description, the specification needs to provide specific guidance on the modified galactose-binding lectin, the membrane translocation domain, and the linkage of three components to be considered enabling for variants.

(4). Predictability or unpredictability of the art:

The claims encompass an agent comprising a galactose-binding lectin or a modified galactose-binding lectin, the L chain of a clostridial toxin or its functional fragment, and a membrane translocation domain, wherein the three components are linked together, a method for obtaining the agent and a method of controlling the transmission of sensory information or the sensation of pain by administering the agent. However, the specification does not identify the modified galactose-binding lectin and the agent containing three components being linked in a different order, it is unpredictable whether these agents would produce similar effect as the agent of ExL-LH_N/A.

(5). The amount of direction or guidance presented and the quantity of experimentation necessary:

The claims are directed to an agent comprising a galactose-binding lectin or a modified galactose-binding lectin, the L chain of a clostridial toxin or its functional fragment, and a membrane translocation domain, wherein the three components are linked together, a method for obtaining the agent and a method of controlling the transmission of sensory information or the sensation of pain by administering the agent. The specification indicates membrane translocation domain may be non-clostridial origin (page 10, lines 20-34) and the production of the agent such as ExL-LH_N/A (Example 1), EcL-LH_N/A (Example 2) and SBA-LH_N/A (Example 3). However, the specification fails to identify the modified galactose-binding lectin, to use a membrane translocation domain of a non-clostridial origin, and to identify an agent containing the three components linked in different orders, which have been indicated in the claim. Moreover, the specification does not demonstrate the claimed method has used such agents. There are no working examples of using these agents in the claimed method. Since the specification does not provide any specific guidance on the identities of modified galactose-binding lectin and of an agent containing the three components linked in different orders and the effects of these agents in the method of controlling the transmission of the sensation of pain, it is necessary to have additional guidance on these agents and to carry out further experimentation to assess the effects of these agentsin the claimed method.

(6). Nature of the Invention:

The scope of the claims includes an agent comprising a modified galactose-binding lectin, a L chain of a clostridial toxin or its functional fragment, and a membrane translocation domain of non-clostridial origin, wherein the three components are linked together, but the specification does not identify the modified galactose-binding lectin and the agent having three

components linked in different orders, nor indicates the use of these agents in the claimed method. Thus, the disclosure is not enabling for the reasons discussed above.

In summary, the scope of the claim is broad, while the working example does not demonstrate the claimed variants, and the guidance and the teaching in the specification are limited, therefore, it is necessary to have additional guidance and to carry out further experimentation to assess the effects of these agents.

In response, applicants argue that the specification has disclosed a reasonable amount guidance regarding the L-chain functional fragments and the tests for functional fragments (pages 13-16 of the response), the agent of a galactose-binding lectin, the L chain of a clostridial toxin or its functional fragment, and a membrane translocation domain of clostridial neurotoxin can be produced recombinantly (pages 19-26), the method of preparing of ExL-LH_N/A, EcL-LH_N/A and SBA-LH_N/A (pages 17-19), and the method of analgesic effects of ExL-LH_N/A and SBA-LH_N/A (pages 26-30 of the response). Applicants further provide additional experimental data for recLH_N/A-ExL in mouse hot plate model to indicate the utility of the agent. The argument is found persuasive, thus withdraw the rejection regarding this subject matter. However, regarding the modified galactose-binding lectin (page 26, paragraph 3), and the preparation of an agent containing the three components which are linked in various together (pages 17-18), the argument is not persuasive because the specification has not provided the guidance on the modified galactose-binding lectin and the agent having the three components linked in different orders, e.g., L-lectin-H_N, without such guidance, it would be necessary to carry out further experimentation to asses the effect of the agent as indicated in the section above..

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-16, 18-54 and 58-61 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-16, 18-54 and 58-61 are indefinite for because of the use of the term "wherein the galactose-binding lectin, L-chain or fragment, and molecule or domain with membrane translocating activity are linked together". The term "wherein the galactose-binding lectin, L-chain or fragment, and molecule or domain with membrane translocating activity are linked together" renders the claim indefinite, it is unclear how the three components are linked, e.g., is the N-terminus of lectin linked to the N-terminus of the peptide including L-chain and H_N chain (lectin-LH_N), or the N-terminus of lectin linked to the N-terminus of H_N chain and then to the L-chain (lectin-H_N-L), or the L-chain linked to lectin and then to H_N chain (L-lectin-H_N)? The specification indicates SPDP (a linking agent for amino group) is used for linking ExL and LHN/A (Example 1, page 13), however, it does not specify which amino group (at N-terminus or lysine side chain) in the peptide is modified by SPDP, thus it is not apparent how the two peptides are linked. Claims 2-16, 18-54 and 58-61 are included in the rejection for being dependent of a rejected claim and not correcting the deficiency of the claim from which they depend.

6. Claims 2, 20-24, 32-34 and 48 are indefinite because the claim does not further limit the claim (claim 1) which they depend from, the membrane translocation domain is part of the heavy

chain of a clostridial toxin, thus it is narrower than the parent peptide. Claims 20-24, 32-34 and 48 are included in the rejection for being dependent of a rejected claim and not correcting the deficiency of the claim from which they depend.

Claims 2, 32-34 and 48 are also indefinite because of the use of the term "the membrane translocation domain is a heavy chain of a clostridial toxin. The term "the membrane translocation domain is a heavy chain of a clostridial toxin" renders the claim indefinite, it is unclear how the agent having both galactose-binding lectin as a targeting moiety and H_C component, a native targeting moiety, binds to the motor neurons?

7. Claims 20-23 are indefinite because of the use of the term "modified to remove or reduce the native binding affinity of the H-chain for motor neurons", "H-chain has been contacted with a derivatising chemical to.....neurons", "H-chain has been mutated by the inclusion of at least one amino acid deletion, insertion, and/or substitution...neurons", or "H-chain has been contacted with a proteolytic agent....neurons". The terms cited above render the claim indefinite, it is unclear how H-chain is modified to reduce the native binding affinity of the H-chain for motor neurons, what compound is used for the modification as to "a derivatising chemical" or "proteolytic agent", and how many amino acids and which residues are deleted, inserted or substituted as to "mutated by the inclusion of at least one amino acid deletion, insertion, and/or substitution". See also claims 42 and 43 as to "at least one amino acid insertion, deletion, or substitution" or "at least one nucleotide deletion, insertion, and/or substitution".

8. Claim 22, 39, 40 and 43 are also indefinite because of the use of the term "and/or". The term "and/or" renders the claim indefinite, it is unclear whether the limitation after "and/or" is included or not, and if included is to be read as an alternative "or" or the conjunctive "and".

9. Claims 37, 40 and 47 are indefinite because of the use of the term "at least one spacer region". The term "at least one spacer region" renders the claim indefinite, it is unclear how many spacer regions are between two components.

10. Claims 51-54 and 58-61 are indefinite because they lack essential steps as claimed in the process of controlling the transmission of sensory information. The omitted steps are: the site and method for administration, the subject receiving the administration of the agent and a step whereby the desired outcome can be determined.

In response, applicants indicate the effective amount has been added in the claim, and the method of administration has been added in claims 58-61. However, claims 51-54 do not cite the method of administration and the outcome of method.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 1-2, 4-16, 20-41, 44-48 and 50-54 are rejected under 35 U.S.C. 102(b) as being anticipated by Foster *et al.* (WO 96/33273).

Foster *et al.* teach an agent containing lectin (page 13, lines 9-13) as the TM component and a modified clostridial neurotoxin such as LH_N (including L-chain and its functional

fragment, claims 1, 4-16, 24-31, 35, 39, 46, 50), the clostridial neurotoxin having H_C chemically modified to reduce its ability to bind the receptor (claims 2, 20-23, 36, 48), a hybrid molecule of a modified heavy chain (H_C being modified) of a clostridial toxin with a light chain of a different clostridial toxin (page 13, line 18-page 14, line 19; claims 32-34) can be obtained by covalently attachment of a TM to a modified clostridial neurotoxin using linkage including one or more spacer regions (page 14, lines 1-9; claim 37, 40, 47) or can be expressed recombinantly as a fusion protein (page 14, line 29-page 15, line 4; claim 38, 41, 50). This agent can bind to a binding site on the surface of sensory neurons (page 12, lines 25-28) and reduce and preferably prevent the transmission of pain signals from nociceptive afferents to projection neurons (page 7, lines 15-17; claims 44-45), therefore it can be used for controlling the transmission of sensory information or pain signals from a nociceptive afferent to a projection neuron (claims 51-54). The agent can be administered by epidural or intrathecal injection (page 16, lines 12-15; claims 58-61).

Note that the lectin indicated in the reference of Foster *et al.* is generic to a plurality of different species, thus it would include the lectin that binds galactose.

In response, applicants indicate Foster *et al.* do not teach a specific targeting moiety such as a galactose-binding lectin. The argument is not found persuasive because Foster *et al.* disclose lectin as a generic term which would include different species of lectin, and it appears that the conjugate of lectin and modified clostridial toxin has the same function as the agent of the present invention.

Conclusion

12. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (703) 308-9437. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, Ph. D. can be reached on (703) 308-2923. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-0294 for regular communications and (703) 308-4227 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Chih-Min Kam, Ph. D. CMK
Patent Examiner

Karen Cochrane Carlson PhD

KAREN COCHRANE CARLSON, PH.D
PRIMARY EXAMINER

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March 15, 2002